respectively 24 months since occurrence of cranial disease manifestation in line with a considerable quality of life improvement asks to investigate more systematically the best use of targeted therapies after whole brain irradiation.

P3-156 NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

Different EGFR mutation patterns are associated with survival and response to first-line chemotherapy in NSCLC

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Purpose: EGFR mutations define a subset of NSCLC with sensitivity to gefitinib or erlotinib. However, all EGFR mutations are not equal and may have different predictive and prognostic value. In this study we compared classical "hot spot" and "rare" EGFR mutations in terms of response to 1st line chemotherapy and overall survival in a cohort of patients with advanced NSCLC.

Patients and Methods: Tumor samples were formalin fixed paraffin-embedded tissues that were microdissected to achieve purity 80% in cancer cells. EGFR mutations were analyzed by DNA sequencing of exons 18 to 21 in both forward and reverse directions in PCR products from tumor genomic DNA.

Results: Of the 169 patients assessable for mutation detection we found 12 (7%) positive for classical "hot spot" (G719D, Del 19, E746V, L747S, L858R) EGFR mutations and 34 (20%) positive for "rare" EGFR mutations. Classical but not rare mutations were associated with female gender and never smoking history (P=0.002; P<0.001 and P=0.637; P=0.402, respectively). However, the histological type had no significant association with either type of EGFR mutations (P=0.520 and P=0.260, respectively).

Response rates to first-line chemotherapy were significantly higher in patients bearing classical mutations (60%) but not in those with rare EGFR mutations (29%) as compared with patients with wild-type EGFR (20.4%) (p=0.005 and p=0.311, respectively). Time to tumor progression was 65 weeks, 22 weeks and 33 weeks for patients with classical mutations, rare EGFR mutations and wild type EGFR, respectively (p=0.165 and p=0.327 as compared to wild type). Overall survival was longer in patients bearing classical mutations (p=0.006) but not in those with rare mutations (p=0.843) as compared to patients with wild type EGFR.

Conclusions: Different EGFR mutation patterns are associated with higher response to first-line chemotherapy and longer overall survival in patients with advanced NSCLC.

P3-157 NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

Correlation of EGFR mutation status between primary tumor and metastases in NSCLC

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Background: EGFR mutations in non-small-cell lung cancer (NSCLC) are associated with sensitivity to gefitinib and erlotinib. However, the correlation of EGFR mutation status between primary tumor and metastases is not established. To investigate this, we analyzed 18 patients with paired samples of primary and metastatic NSCLC.

Methods: Tumor metastases include adrenal gland, liver, bone, brain, lung, skin and thoracic wall. All tumor samples were formalin fixed paraffin-embedded tissues. Exons 18, 19, 20 and 21 of the EGFR were amplified by PCR and the products were directly sequenced on an ABI 3100 Avant genetic analyzer. All mutations were confirmed by sequencing in both directions and by an independent PCR amplification.

Results: In 12 cases there was concordance between the primary tumor and the corresponding metastases, with EGFR status determined as wild type. Discordance was observed in six cases (33.3%): in three cases EGFR was mutated only in the primary tumor, while in two cases EGFR mutations were found only in metastases. Finally, in one patient the metastases had an additional mutation besides that of the primary tumor. Two out of 18 patients carried the L692P-V717A and T847A mutations respectively only in their metastases. The time to tumor progression (TTP) in 1st line chemotherapy was 29 weeks for the patient carrying the double mutation (L692P-V717A) and 307 weeks for the patient carrying the T847A mutation. Seven out of 18 patients were treated with gefitinib. Three of them had no mutations in both the primary and metastatic tumors and the median TTP was 20 weeks. Three patients carried the E746V, L692P and G857E mutations, respectively, in their primary tumors but were wild type in their metastases. Interestingly, these patients received RTK inhibitors prior to developing the metastases. The median TTP for them was 59 weeks. The last patient who carried the Del 19 in his primary tumor and the Del 19 and T790M in his metastases received gefitinib before the second surgery and exhibited TTP of 80 weeks.

Conclusions: Our findings suggest a discordance of EGFR mutation status between primary tumor and metastases and imply a possible role for EGFR mutation analysis of metastases for the treatment of metastatic NSCLC with RTKIs.

P3-158 NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

A prospective study assessing tumor response of gefitinib in chemonaive good performance advanced stage nonsmall cell lung cancer (NSCLC) patients with different types of Epidermal Growth Factor Receptor (EGFR) mutations

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Background: Gefitinib is an effective treatment for chemotherapy-resistant East Asian NSCLC patients. The efficacy of gefitinib in chemonaive NSCLC patients bearing different types of EGFR mutations in their tumor tissue and who are candidates for standard chemotherapy is unclear. It is important to know the precise response rates and response durations of gefitinib in these patients in order to compare this novel approach with standard chemotherapy.

Methods: A phase II study was designed to collect gefitinib anti-tumor efficacy information of advanced stage NSCLC patients. Eligibility criteria included histological or cytological proven chemonaive stage IIIB/IV NSCLC, measurable disease, ECOG performance status of 0-2, good organ functions and candidates for platinum-based chemotherapy. Patients were treated with 250mg gefitinib per day. Tumor assessments were performed every two months by RECIST criteria. Responding or stable patients were treated until progression. To avoid bias in the objective response assessment, tumor samples were collected and tested for EGFR mutation when most patients were progressed on the treatment. Therefore, investigators were blinded to the tumor EGFR mutational status results when tumor responses were assessed. A radiologist independently reviewed all scans of the responding patients. Simon's two-stage design was used to aim at a response rate more than 20%. A total of 106 patients were planned.

Results: There were 38 men and 68 women. Median age was 66.7 (range 32.3-86.2). ECOG performance status of 0/1/2 were 0/98/8. There were 75 /19 / 12 patients who were nonsmokers / quitted for 1 year / current smokers. Ninety-seven (91.5%) patients had adenocarcinoma histology. Investigator-assessed tumor responses are presented here. There were 1/58/29/14/4 patients with CR/PR/SD/PD/NE. Overall response rate was 55.7% (95% confidence interval 46.2-65.2%) and disease control rate was 81.1%. EGFR gene mutation analyses were performed in 83 patients' tumor samples using polymerase chain reaction amplification and direct DNA sequencing. Mutations of exons 18, 19, 20, 21(L858R), 21(other mutations) were detected in 1/19/6/19/6 patients. The response rate and duration of 19 patients with del 19 were 94.7% and 11.8 months. The response rate and duration of 19 patients with L858R mutation were 84.2% and 11.5 months. The response probabilities in patients with other mutations were low. The response rate for 32 patients with wild type EGFR was 28.1%. The response rate was 65.2% in 23 patients whose EGFR mutation test were not performed. The response rates and durations of patients with different types of EGFR mutations using independent review results will be presented in the meeting.

Conclusions: Consistent high response rates and long response durations were observed in chemonaive good performance advanced stage NSCLC patients with deletion 19 or L858R mutations of EGFR in their tumor samples. In a good-predictive -factor enriched population, the response rate were still higher than or comparable to patients receiving chemotherapy if EGFR was tested wild type in their tumor samples or if mutation test can not be performed.

P3-159 NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

Epidermal growth factor receptor mutation in chinese patients with non-small cell lung

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Background and Objective: Recent studies showed that somatic mutations in epidermal growth factor receptor(EGFR) tyrosine kinase(TK) domain are associated with sensitivity of non-small cell lung cancer(NSCLC) to TK inhibitor. This study was to analyze EGFR mutations in patients with NSCLC. Method: Specimens of lung cancer were collected from 90 consecutive NSCLC patients DNA was extracted from the 90 specimens.Exons19 and 21 were amplified by polymerase chain reaction (PCR), and sequenced and analyzed from both sense and antisense directions.

Result: Somatic mutations in TK domain of EGFR in tumors were identified from 26 of the 90(28.9%)patients, including 16 cases(64.0%) of in-frame deletion in exon 19 and 9 cases(36.0%) of amino acid substitution in exon 21. Mutation rate was significantly higher in adenocarcinoma and bronchioalveolar carcinoma than in squamous cell carcinoma[13/35(37.1%),and 90.0%(9/10) vs. 4/45(8.9%),P<0.0001],: and significantly higher in non-smokers than in smokers[18/36(50%) vs 8/54(14.8%),P=0.001].: Mutation rate in women was also higher than in men [15/25(60%) vs 11/65(16.9%),P<0.0001]: Mutations rate in patients with advanced lung cancer(III, IV stage) are higher than that in early stage(I, II stage)[15/71(21.1%) vs 11/19(57.9%),P=0.004]: But there is no significant difference in the patients of different age(<70y or .≥70y) [17/62(27.4%) vs 9/28(32.1%), P=0.534].

Conclusion: EGFR mutation rate in Chinese NSCLC patients is high. Adenocarcinoma (bronchioalveolar carcinoma in particularly), non-smoker, femal patients and patients with advanced lung cancer are four important factors to predict EGFR mutation.

P3-160 NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

Histoculture drug response assay for gefitinib in non-small cell lung cancer

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Gene mutations in the ATP binding site of EGFR is a well-known predictive factor for chemosensitivity of gefitinib. However, several additional predictive factors for gefitinib sensitivity were reported, i.e., EGFR copy number, k-ras mutation, and the other erbB family molecules. To investigate all of these predictive factors is too expensive. Therefore, we are now trying to evaluate chemosensitivity for gefitinib in non-small cell lung cancer, using an in vitro drug sensitivity test.

Materials and Methods: Surgically resected fresh tumor specimens obtained from the 22 patients with non-small cell lung cancer were used. There were 13 males, 9 females, ranging in age 49-84 (average 70) years old. Sixteen patients (73%) were smokers. Sixteen adenocarcinoma, 4 squamous cell carcinoma, 1 lymphoepithelioma-like carcinoma, and 1carcinoid were included. Histoculture drug response assay (HDRA) were used as an in vitro drug sensitivity test. HDRA technique was the same as we previously reported (JTCVS 133: 303-8, 2007). Small pieces of viable cancer tissue was placed on the collagen gel, and then cultured 7 days in the presence of the gefitinib. Concentrations of gefitinib were 5, 10, 20, and 40 μg/ml. MTT assay was used to evaluate the viability of cancer tissue after incubation. The inhibition rate was calculated by using the following formula.

Inhibition rate (%) = (1 - mean absorbance of treated tumor/weight / mean absorbance of control tumor /weight) x 100.

Results: Assay was successful in all specimens. Average inhibition rates at the concentration of 5, 10, 20, and 40 μg/ml were 8.4%, 9.8%, 16.9%, and 45.8%, respectively. Dose-response relationship was observed between the inhibition rates and the gefitinib concentrations (p=0.02). In 4 patients, the inhibition rate was evaluated only at the concentration of 20 μg/ml (I20).